fig. 1a: Observed (green) and predicted (red) cumulative incidence of grade 2+ esophagitis versus the V50Gy in the esophagus.

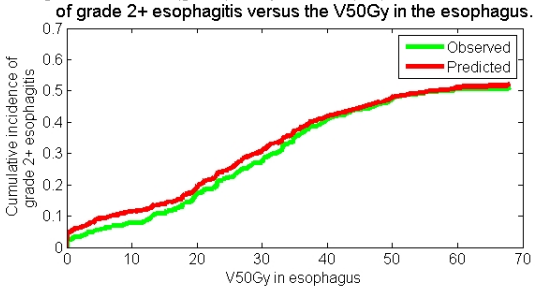
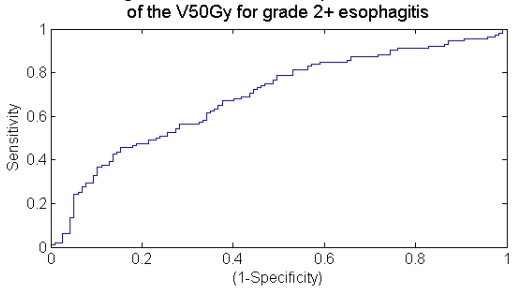


fig. 1b: ROC curve for the predictive value of the V50Gy for grade 2+ esophagitis



Conclusion: The observed and predicted dose-effect of grade ≥2 esophagitis were almost identical. This implies that our esophagus dose parameter accurately predicts toxicity for our current patient population and treatment protocol. This result is surprising, since esophagitis incidence was expected to decrease because of the introduced pre-hydration. While the origin of this discrepancy requires further investigation, it does show that the electronic toxicity scoring system and connection to the dose parameters appears to be a useful and valuable tool to audit the applicability of dose constraints in daily clinical practice.

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Impact of radiation induced cell death kinetics on reoxygenation and tumour response.

A. Gago-Arias[1], I. Espinoza[1], B. Sánchez-Nieto[1], J. Pardo-Montero[2]
[1]*Pontificia Universidad Católica de Chile, Institute of Physics, Santiago, Chile*
[2]*Clinical University Hospital, Department of Medical Physics, Santiago de Compostela, Spain*

Purpose or Objective: The radiosensitivity of cells has an oxygen dependence that leads to an undesired resistance of hypoxic tumour cells. This is well known[1] and the linear quadratic response model has been extended to account for it.[2] In order to properly model tumour responses, the information about the distribution of oxygen at a microscopic scale must be available.[3] Modelling works usually derive this distribution by solving the reaction-diffusion equation in a voxelized tumour geometry that includes a vascularization distribution model.[4] However, the oxygen available to the cells increases during radiotherapy due to, among other factors, cell killing. This reoxygenation process can turn hypoxic cells into oxic, changing the cells radiosensitivity during the treatment. In this work we implement two models of cell death kinetics, CDKM, to analyse how they affect reoxygenation and hence the response of tumours to radiotherapy.

Material and Methods: Two CDKMs are compared:
a) Delayed cell killing model, DCDKM: The number of dead cells after irradiation varies with time according to an exponential expression. Cells can die shortly or long after irradiation, mimicking early and late apoptosis.
b) Instantaneous cell killing model, ICDKM: Cell death occurs immediately after irradiation (early apoptosis scenario).
Using these models, oxygen distributions are recomputed before the delivery of each fraction, considering the decrease in oxygen consumption due to cell death caused during the previous fractions. The oxygen consumption can be computed globally, by voxel averaging surviving fractions, or locally, at a subvoxel scale. The differences in reoxygenation and tumour response arising under different CDKM and oxygen consumption scenarios depend on the vascular fraction, VF, and the fractionation scheme. This was illustrated for a conventional schedule and a hypofractionated treatment.

Results: In the conventional treatment, the doses needed to achieve 50% tumour control (D50) are ~ 10 and 2 Gy larger under the ICDKM (for VFs of 1% and 3%, respectively). Differences are larger in the hypofractionated scheme, for which the TCP remains equal to zero under the DCDKM for a VF equal to 1%. For a VF equal to 3%, D50 values are ~ 20 Gy larger under the DCDKM. Similar results were found under the global and local oxygen consumption calculations.

Conclusion: This work shows that the kinetics of cell death can have a great impact in the simulation of reoxygenation and tumour response. Radiation response models should account for cell death kinetics to properly evaluate tumour response, especially in hypofractionated schemes.

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Estimation of tumor radio-sensitivity using mathematical models and analysis of the oxygenation role

A. Belfatto[1], D.A. White[2], R.P. Mason[2], Z. Zhang[3], S. Stojadinovic[3], G. Baroni[1], P. Cerveri[1]
[1]*Politecnico di Milano University, DEIB, Milano, Italy*
[2]*The University of Texas Southwestern, Radiology, Dallas, USA*
[3]*The University of Texas Southwestern, Radiation Oncology, Dallas, USA*

Purpose or Objective: The project aims at predicting tumor radiation starting from pre-treatment information related to cancer volume and oxygenation.

Material and Methods: Eighteen Copenhagen rats, implanted with prostate tumor, underwent two irradiations (2x15Gy). Nine rats were treated in standard conditions (Air), while the remaining group (Oxy) inhaled oxygen. Before the first irradiation, an interleaved blood (BOLD) and tissue (TOLD) oxygen level dependent (IBT) MRI sequence was performed. Four indices were computed, namely, BOLD and TOLD signal intensity variation (dSI), and the change in longitudinal (dR1) and transverse (dR2*) relaxation rate. The tumor volume evolution was monitored by means of weekly caliper measurements. A two-equation system describing the uncontrolled growth and the response to treatment of the active cells population, along with the dead cell clearance dynamics, was implemented in Matlab® (MathWorks, Natick, Massachusetts, USA). Three parameters, namely the volume doubling time, the radiation sensitivity (α) and the dead cell clearance time, were learned on a subject-specific basis using a genetic algorithm. Finally, a feed forward neural network (FF-ANN) was trained (*Fig. 1*) to predict α starting from the MRI indices and initial volume, for each group (Air/Oxy).